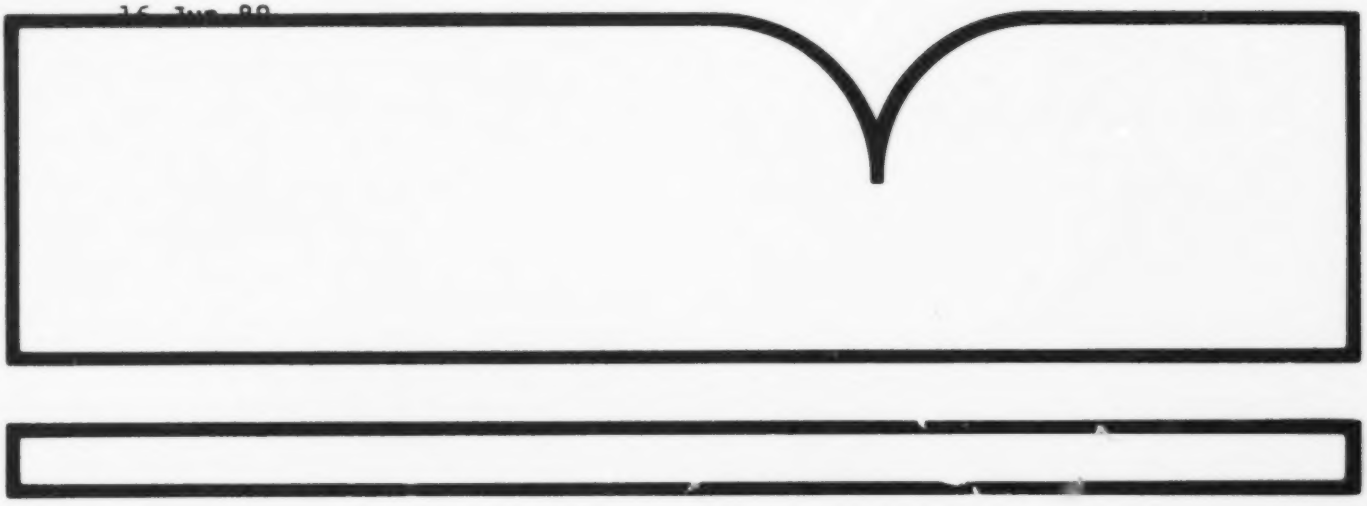
PB92-160548

Pesticide Fact Sheet Number 232: Isoxaben

(U.S.) Environmental Protection Agency, Washington, DC

16 Jun 89



U.S. Department of Commerce
National Technical Information Service
NTIS

50272-101

REPORT DOCUMENTATION PAGE	1. REPORT NO.	2.	PB92-160548

4. Title and Subtitle EPA Pesticide Fact Sheets - Isoxaben No. 232	5. Report Date June 16, 1989 6.
7. Author(s) EPA, Office of Pesticide Programs, Registration Division	8. Performing Organization Rept. No. 540/FS- 92-188
9. Performing Organization Name and Address U.S. Environmental Protection Agency Office of Pesticide Programs Registration Division (H7505C) 401 M Street, SW Washington, D.C. 20460	10. Project/Task/Work Unit No. 11. Contract(C) or Grant(G) No. (C) (G)
12. Sponsoring Organization Name and Address Same as #9	13. Type of Report & Period Covered 14.

15. Supplementary Notes

16. Abstract (Limit: 200 words)

This document contains up-to-date chemical information, including a summary of the Agency's regulatory position and rationale, on a specific pesticide or group of pesticides. A Fact Sheet is issued after one of the the following actions has occurred.

1. Issuance or reissuance of a registration standard,
2. Issuance of each special review document,
3. Registration of a significantly changed use pattern,
4. Registration of a new chemical, or
5. An immediate need for information to resolve controversial issues relating to a specific chemical or use pattern.

17. Document Analysis a. Descriptors

Pesticides, regulations, Chemical Information Fact Sheet, Use Patterns, science findings.

b. Identifiers/Open-Ended Terms

c. COSATI Field/Group

18. Availability Statement:	19. Security Class (This Report)	21. No. of Pages
Publicly Available	Unclassified	7
	20. Security Class (This Page) Unclassified	22. Price

PB92-160548

United States
Environmental Protection
Agency

Office of Pesticides and Toxic Substances
Office of Pesticide Programs (TS-766C)
Washington, DC 20460

540/FS-92-188

EPA

Pesticide Fact Sheet

Name of Chemical: Isoxaben
Reason for Issuance: New Chemical Registration
Date Issued: June 16, 1989
Fact Sheet Number: 232

1. Description of Chemical

Generic Name: N-[3-(1-ethyl-1-methylpropyl)-5-isoxazolyl]-2,6-dimethoxybenzamide and Isomers
Common Name: Isoxaben
Trade Name: Gallery
EPA Shaughnessy Code: 125851
Chemical Abstracts Service (CAS) Number: 82558-50-7
Year of Initial Registration: 1988
Pesticide Type: Herbicide
U.S. and Foreign Producers: Elanco Products Company
Division of Eli Lilly and Company
P.O. Box 708
Greenfield, IN 46140

2. Use Patterns and Formulations

Application Sites: Established turf, landscape ornamentals, container grown ornamentals, ground covers, nursery stock, nonbearing fruit and nut crops, nonbearing vineyards, and noncropland (industrial sites, utility substations, highway guardrails, signposts, and delineators).

Types of Formulations: 75% Dry Flowable (DF) End-Use Product

Types and Methods of Application: End-use product is applied by ground application. Preemergent activity prevents germination of certain broadleaf weeds and annual grasses.

Application Rates: 1/4 to 1 lb ai/A

Usual Carrier: Water

3. Science Findings

Summary Science Statement: Isoxaben has been found to be oncogenic in mice and has been classified as a Group C oncogen (possible human carcinogen). Evidence was not considered sufficient to

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warrant a quantitative estimate of risk for isoxaben, for the following reasons: The oncogenic response was in one species only; tumor incidence was statistically increased at the high dose only; the tumors were of a common type; were predominantly benign; and there was no decrease in latency.

Isoxaben is not considered to be teratogenic and the chemical did not significantly impair reproductive ability in a two-generation reproductive effects study in rats.

Four mutagenicity studies with isoxaben were negative. A mouse micronucleus study showed a statistically significant increase in micronuclei formation at all doses.

Isoxaben is not acutely toxic to mammalian or avian species or honey bees. The pesticide is moderately toxic to freshwater fish and invertebrates. A minimum adverse effect is expected on nontarget organisms. Isoxaben is stable to hydrolysis but is photolabile. Isoxaben is not mobile; however, it is persistent. Isoxaben and its degradates demonstrate a low potential to leach into groundwater.

Chemical Characteristics: (Isoxaben Technical)

Color: White to off white
Physical State: Crystalline solid
Odor: No appreciable odor
Melting Point: 176 to 179 °C
Specific Gravity: 0.52 to 0.56 g/mL
Solubility:

H_2O	1 ppm
Acetone	5 g/100 mL
Acetonitrile	3 g/100 mL
Chloroform	5 g/100 mL
Dichloromethane	5 g/100 mL
Ethylacetate	5 g/100 mL
Methanol	5 g/100 mL
Xylene	0.4 g/100 mL
Hexane	0.007 g/100 mL

Vapor Pressure: Less than 3.9×10^{-7} mm Hg at 26 °C
Dissociation Constant: No titratable group in 66% DMF between pH 3.5 and 13.3
Octanol/Water Partition Coefficient: $K_w = 434$, Log $K_w = 2.64$
pH: 3.0
Stability: Relatively stable

Toxicology Characteristics:

Acute Effects:[1/]

- o Acute Oral Toxicity (Rat): > 10,000 mg/kg (Technical); > 5,000 mg/kg (75% DF); Toxicity Category IV
- o Acute Dermal Toxicity (Rabbit): > 200 mg/kg (Technical); > 5000 mg/kg (75% DF); Toxicity Category III
- o Primary Eye Irritation (Rabbit): Corneal dullness, slight iritis and conjunctivitis - All treated eyes normal within 72 hours (Technical); Irritation cleared in 7 days except one animal which cleared in 14 days (75% DF); Toxicity Category III
- o Primary Skin Irritation (Rabbit): No irritation from 200 mg/kg (Technical); Slight irritation which cleared within 5 days (75% DF); Toxicity Category III
- o Acute Inhalation: > 1.99 $\pm$ 0.199 mg/L (Technical); Toxicity Category II
- o Dermal Sensitization: Not sensitizing

Subchronic Effects:

- o 90-Day Feeding Toxicity Study (Mice): Lowest-effect level (LEL) was 1400 ppm. The no-observed-effect level (NOEL) was 100 ppm. Liver hypertrophy in males, increased liver weight and liver induction in males and females occurred at LEL and highest dose tested (HDT) (12,500 ppm).
- o 90-Day Feeding Toxicity Study (Dogs): LEL = 1000 mg/kg/day; NOEL = 110 mg/kg/day; Increased liver weight, liver/body weight ratio at LEL (HDT).
- o 21-Day Dermal Toxicity Study (Rabbits): Showed very slight irritation. The NOEL was < 1055 mg/kg/body weight (only level tested).

Chronic Effects

Chronic Feeding/Oncogenicity (Rats): In a 2-year feeding study in Fischer 344 rats at doses of 0, 125, 1250, and 12,500 ppm in the diet, the systemic LEL was 1250 ppm and systemic NOEL was 125 ppm. Nononcogenic effects included dose-related

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1/ See 40 CFR 156.10 for discussion of toxicity categories and companion labeling requirements.

increase in progressive glomerulonephoesis (high-dose females and mid- and high-dose males), effects on the stomach mucosae and heart (considered to be sequelae of the kidney effects), parathyroid hyperplasia; increased BUN and creatinine (also reflecting the kidney change); and increased trend in mortality for male rats. There was an increase in benign adrenal pheochromocytomas in high-dose males, which was not statistically significant when compared to controls; however, a positive trend was detected.

Chronic Feeding/Oncogenicity (Mice): In a 2-year feeding study in B6C3F1 mice at doses of 0, 100, 1000, and 12,500 ppm in the diet, the systemic LEL was 1000 ppm and the systemic NOEL was 100 ppm. Nononcogenic effects included lowered body weight and body weight gain in males, hepatocellular vacuolation, hepatocellular hyperplasia, and hepatocytomegaly. There was a significant increase in hepatocellular adenomas for both sexes at the high dose and in combined hepatocellular adenomas/carcinomas in females at the high dose. A significant dose-related trend for hepatocellular adenoma and for combined hepatocellular adenoma/carcinoma was observed in both sexes.

Developmental Toxicity: Rats were dosed with 0, 100, 320, and 1000 mg/kg/day. The maternal LEL was 1000 mg/kg/day with decreased body weight gain and the maternal NOEL was 320 mg/kg/ day. The developmental LEL was 1000 mg/kg/day (HDT) with increased preimplantation loss, increased resorptions, smaller litter size, and increased number of runt fetuses. The Developmental NOEL was 320 mg/kg/day.

Rabbits were dosed with 0, 100, 320, and 1000 mg/kg/day isoxaben in the diet. The maternal and developmental NOEL was greater than 1000 mg/kg/day (HDT).

Three-Generation Reproduction (Rat): Wistar-strain rats were dosed with 0, 500, 2500, and 12,500 ppm isoxaben in the diet. The maternal LEL was 2500 ppm with lowered body weight and body weight gains and increased liver/body weight ratio in both sexes. The NOEL was 500 ppm. The reproductive LEL was 12,500 ppm (HDT) with decreased number of viable pups and lowered body weight of progeny on postpartum day 21. The developmental LEL was 12,500 ppm (HDT) with decreases in viable fetuses per litter and increased hydroureter and microphthalmia.

Mutagenicity: The Ames study was negative, with and without metabolic activation. DNA repair in adult rat hepatocytes was not positive. A cytogenetic assay using CHO cells was negative for induction of chromosomal aberrations. An SCE assay using Chinese hamster bone marrow was negative in demonstrating genotoxic potential. A mouse micronucleus study using only

males showed a significant increase in micronuclei formation at all doses.

Physiological and Biochemical Characteristics:

Mechanism of Pesticidal Action: Isoxaben reduces seedling germination.

Environmental Characteristics:

Persistence: Isoxaben is stable to hydrolysis. With natural sunlight isoxaben in sterile aqueous solution had a half-life of 7 to 15 days. In aerobic soils the half-lives were 4.3, 5.6, and 10.6 months, respectively, for clay loam, loam, and sandy loam soils. In a field dissipation study the half-life was from 66 to 106 days.

Adsorption and Leaching: Isoxaben is not mobile in column leaching studies using worst-case conditions. Its degradate is slightly mobile. Adsorption/desorption study in sandy loam soil reported a K_d value of 5.7 mL/g, indicating isoxaben is not a mobile chemical. In a field dissipation study, isoxaben and its major degradate remained in the top 0 to 12 inches of soil over the 313-day sampling period.

Bioaccumulation: Isoxaben was found to accumulate in bluegill sunfish up to 14X in edible tissue (fillet), 134X in nonedible tissue, and 70X in whole fish. Accumulated residues were depurated rapidly.

Environmental Fate and Surface and Groundwater Contamination Concerns: Isoxaben is not mobile; however, it is persistent. Isoxaben and its degradates demonstrate low potential to leach into groundwater.

Ecological Characteristics:

Avian Acute Oral Toxicity (Bobwhite Quail - LD_{50}): > 2000 mg/kg
Avian Subacute Dietary Toxicity (Bobwhite Quail and Mallard Duck - LC_{50}): > 5000 ppm
Avian Reproduction: Mallard Duck: NOEL = 300 ppm; LEL = 1000 ppm (reduction in hatchability of eggs); Bobwhite Quail: NOEL = 1000 ppm (highest level tested)
Freshwater Fish Acute Toxicity (Rainbow Trout and Bluegill Sunfish - LC_{50}): > 1.1 ppm (maximum solubility of isoxaben in water)
Freshwater Fish Early Life Stage: Fathead Minnow: NOEL = 0.4 ppm (highest level tested) - Rainbow Trout: NOEL = 0.42 ppm (highest level tested)
Freshwater Fish Early Life Stage - Rainbow Trout: NOEL = 0.42 ppm (highest level tested)
Freshwater Invertebrate Acute Toxicity (Daphnia magna - LC_{50}): > 1.3 ppm (maximum solubility)
Freshwater Invertebrate Life Cycle (Daphnia magna): NOEL = 0.69 ppm; LEL = 1.01 ppm (statistically significant effects on growth and brood size)

Estuarine and Marine Organism Acute Toxicity: Quahog Clam (Embryo-larvae EC_{50}) > 0.96 ppm (maximum solubility) (40% effect at this level); Grass shrimp LC_{50} > 1 ppm (maximum solubility); Sheepshead Minnow LC_{50} > 0.87 ppm (maximum solubility)
Honey Bee Acute Toxicity: > 101.7 ug/bee

These data indicate that isoxaben is practically nontoxic to avian species and honey bees, and is moderately toxic to fish and aquatic invertebrates. Minimal adverse acute and chronic effects are expected to nonendangered and endangered terrestrial and aquatic organisms.

Tolerance Assessment:

There are no registered food or feed uses for isoxaben that require the establishment of tolerances.

4. Contact Person at EPA

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